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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,353	04/27/2001	Gary Ruvkun	00786/351005	3561

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,353	RUVKUN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,12,13 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,12,13 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 06/04/04 has been acknowledged.

Claims 1, 4, 12-13, 16-20 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***703-872-9306****.*

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/04/04 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 12-13 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method for screening candidate modulatory compounds for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity comprising: providing a C. elegans or isolated C. elegans cell expressing a gene that encodes a variant of SEO ID NO:54 that functions in insulin signaling; and contacting the C. elegans or isolated C. elegans cell with a candidate compound, wherein a decrease in expression or activity of the gene with the candidate compound identifies a candidate modulatory compound for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity.

At best the specification discloses the amino acid sequences of SEQ ID NO:54 which represent an amino acid motif at location 242-344 of *C. elegans* daf-16 protein (spec. page 77, para.2). Based upon the degree of amino acid homology (Spec. fig-21A), the specification teaches that FKHR and AFX are human orthologs of C. *elegans's* daf-16 (Spec. fig-21B). Besides the amino acid sequences of SEQ ID NO:54 the specification as filed fails to disclose any variant of SEQ ID NO:54 that functions in insulin signaling. Similarly the specification as filed fails to disclose any variant of SEQ ID NO:54 that hybridizes under stringent conditions to the nucleic acid encoding the amino acid sequences of SEQ ID NO:54. Besides FKHR and AFX the specification fails to disclose any other variant of SEQ ID NO:54 obtained form any organism or any other human gene are capable of sub serving the same function as C. elegans DAF-16, i.e. transduction of insulin signals and convergence with DAF-7-like Smad signals. However the specification as filed fails to identify the relevant characteristics such that a person skilled in the art would recognize the human FKHR and human AFX genes. For example the specification fails to disclose an amino acid sequence identified by a SEQ ID NO for human FKHR and AFX genes.

Response to arguments

The applicant argues that claims 1 and 17 as amended now recite characteristic functional and structural features of Daf-16 related polypeptides. The applicant argues that the specification has identified DAF-16 as a member of the forkhead family of

transcription factors. The sequence alignment shows that human FKHR and AFX polypeptides share regions having a high degree of sequence identity, in particular, DAF-16, FKHR, and AFX share a characteristic structural motif (SEQ ID NO:54) found within the forkhead DNA binding domain. The applicant argues that the FKHR and DAF-16 are so closely related that the human protein is able to functionally substitute for C. elegans DAF-16 in-vivo. The applicant argues that while the claimed invention encompasses DAF-16 variants that might not share the functional characteristics of DAF-16, given that the human protein is able to functionally substitute for the C elegans polypeptide, one skilled in the art would understand that DAF-16 proteins having at least 85% amino acid sequence identity to SEQ ID NO:54 would also function in insulin signaling. The applicant argues that he has shown that C. elegan DAF-16, human AFX, and human FKHR as species that is clearly representative of the genus as claimed.

However, applicant's argument are found NOT persuasive because the specification fails to disclose any variant of SEQ ID NO:54 that has the functional property of an insulin signaling polypeptide explicitly or implicitly as putatively claimed herein. Applicant were referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only discloses the amino acid sequences of daf-16 (SEQ ID NO:54) and daf-16 human orthologs FKHR and AFX. The specification fails to disclose any variant of SEQ ID NO:54 that has the functional property of an insulin signaling polypeptide explicitly or implicitly as putatively claimed herein.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312,*

48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the nucleic acid variants (as claimed) has been defined only by a statement of function that broadly encompasses an insulin signaling like activity, which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics.

The variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of daf-16 polypeptide. For example 15% variation (85% identical) or hybridization product as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994 ref of record). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976, ref of record). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1, 4, 12-13 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention:

The instant invention relates to a method for identifying a compound that ameliorate or delay an impaired glucose tolerance condition atherosclerosis or obesity.

Breadth of Claims and Guidance Provided in the Specification

The instant claims are drawn to a method for screening candidate modulatory compounds for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity comprising: providing a C. elegans or isolated C. elegans cell expressing a gene that encodes a variant of SEO ID NO:54 that functions in insulin signaling; and contacting the C. elegans or isolated C. elegans cell with a candidate compound, wherein a decrease in expression or activity of the gene with the candidate compound identifies a candidate modulatory compound for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity.

At best the specification discloses the amino acid sequences of SEQ ID NO:54 which represent an amino acid motif at location 242-344 of *C. elegans* daf-16 protein (spec. page 77, para.2). Based upon the degree of amino acid homology (Spec. fig-21A), the specification teaches that FKHR and AFX are human orthologs of C. *elegans's* daf-16 (Spec. fig-21B). Besides the amino acid sequences of SEQ ID NO:54 the specification as filed fails to disclose any variant of SEQ ID NO:54 that functions in insulin signaling. Similarly the specification as filed fails to disclose any variant of SEQ ID NO:54 that hybridizes under stringent conditions to the nucleic acid encoding the amino acid sequences of SEQ ID NO:54. Besides FKHR and AFX the specification fails to disclose any other variant of SEQ ID NO:54 obtained form any organism or any other human gene are capable of sub serving the same function as C. elegans DAF-16, i.e.

transduction of insulin signals and convergence with DAF-7-like Smad signals. However the specification as filed fails to identify the relevant characteristics such that a person skilled in the art would recognize the human FKHR and human AFX genes. For example the specification fails to disclose an amino acid sequence identified by a SEQ ID NO for human FKHR and AFX genes.

State of Art and Predictability

The state of the art at the time filing of instant invention teaches that the analysis of daf-16 cDNAs revealed three alternatively spliced forms, designated daf-16a1, daf-16a2 and daf-16b. DAF-16a and DAF-16b have distinct but highly related Fork head type DNA-binding domains. The amino-terminal half of the DNA-binding domain is encoded by exons 3 and 4 for DAF-16a and exon 5 for DAF-16b. The C-terminal half of each DNA-binding domain is encoded by exons 6 and 7 which are common to both transcripts. The DAF-16a and DAF-16b isoforms are generated from distinct promoters, suggesting that they could be expressed in and mediate DAF-2 signalling in distinct tissues or cell types. Furthermire these isoforms have distinct Fork head DNA-binding domains that interact with distinct partners (i.e. DAF-3, DAF-8 or DAF-14) or may bind to distinct downstream promoters. Thus, the expression and differential splicing of the two distinct DAF-16 Fork head DNA-binding domains is expected to be functionally important but is not obviously implicated in DNA-binding specificity. Furhtermore, within the Fork head DNA-binding domain, DAF-16a is 65% and 62% identical to FKHR and AFX, whereas DAF-16b is 50% and 47% identical to FKHR and AFX genes. In addtion the molecular analysis of other daf-16 mutant alleles revealed that the two major DAF-16 isoforms are not redundant. The identification of daf-16a specific mutations indicates that daf-16b activity is not sufficient to induce dauer arrest in a daf-2 mutant (Ogg et al Nature. 389:994-999, 1997. ref. of record on PTO 1449. see page 995, col.2 para. 2-4; page 996, para.1-2). Thus considering the scope of the instant invention as claimed it is considered highly unpredictable that a 5% variation (85% identical) or any hybridization product obtained form any organism would encode insulin signaling like activity, which is similar to *C. elegans* daf-16 gene. In addition the variation as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such

functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976, ref. of record).

The state of the art regarding the arteriosclerosis teaches that development of the arteriosclerosis is complex and several factors like smoking, diet and exercise, hypercholesterolemia, hypertension, diabetes, and some genetic factors account for much less than 100% of disease. In addition the atherogenic processes resemble many aspects of chronic inflammation, a response that may be promoted by microorganisms, suggesting an infectious etiology (O'Connor et al Emerg. Infect Dis. 5:780-8, 2001). In the instant case the specification fails to provide any guidance regarding the role of daf-16 or its human orthologs AFX and FKHR in the development of arteriosclerosis. Therefore considering the state of the art regarding the development of arteriosclerosis and the limited amount of guidance provided in the instant specification as filed it is unclear how one skill in the art would use a compound that decrease the expression of daf-16 for the ameliorating or delaying atherosclerosis. The specification as filed fails to provide any evidence that establishes the role of daf-16 or its human orthologs in the development of atherosclerosis

Similarly obesity is a complex phenotype which is not only the result of genetic variations but is also the out come of personal behavioral and life style (Lonnqvist et al Nat. Med. 149):950-953, 1995. ref. of record on PTO 1449; see page 951 col.I para.I line 1). Although insulin resistance is usually associated with obesity, leaner subjects can also be found having insulin resistant due to the accumulation of visceral fat. Even thought the Insulin sensitivity and beta-cell function are intimately linked the role of elusive genetic or environmental factor(s) responsible for insulin resistance is still a

matter of debate. Under normal circumstances, insulin secretion by the pancreatic islet b-cell is a complex event, which is modulated by a number of different variables including the nature of the secretagogue, the quantity of the secretagogue administered, the route of administration of the stimulus, the prevailing glucose level at the time of administration of the stimulus and finally, the prevailing degree of insulin sensitivity (Kahn et al. J. Nutr. 131(2):354S-360S. 2001). Therefore considering the state of the art regarding the impaired glucose tolerance and obesity comprising and the limited amount of guidance provided in the instant specification as filed it is unclear how one skill in the art would use a compound that decrease the expression of daf-16 for the ameliorating or delaying impaired glucose tolerance and obesity. The specification as filed fails to provide any evidence that establishes the role of daf-16 or its human orthologs in the development of impaired glucose tolerance and obesity.

Response to arguments

The applicant argues that claims are now limited to screening methods that require a polypeptide having at least 85% amino acid sequence identity to SEQ ID NO:54 and that function in insulin signaling. The applicant argues that the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation. The applicant argues that specification teaches amino acid sequences that may be used to identify a daf-l6 family member present in a sequence database. The applicant argues that he has shown that a daf-16 human homolog when expressed in a worm was able to functionally replace the worm protein.

However, applicant's arguments are found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The scope of invention as claimed encompasses the use of a gene that encodes any variant of SEO ID NO:54 and functions in insulin signaling. Besides the human AFX, and human FKHR orthologs the specification as filed fails to disclose any other variant (85% identical) or any hybridization product that encodes a polypeptide that is capable

of modulating insulin signaling like a daf-16 polypeptide. As stated above the office has clearly provide an evidence that the molecular analysis of daf-16 mutant alleles revealed that the two major DAF-16 isoforms are not identical in function. For example the identification of daf-16a specific mutations indicates that daf-16b activity is not sufficient to induce dauer arrest in a daf-2 mutant. Thus considering the scope of the instant invention as claimed and for the reasons as stated above it is considered highly unpredictable that a 5% variation (85% identical) or any hybridization product obtained form any organism would encode insulin signaling like activity, which is similar to *C. elegans* daf-16 gene. In addition considering the applicant's disclosure it is unclear how one skill in the art would exercise the invention as claimed without further undue amount of experimentation, since the specification as filed fails to provide any evidence which establishes that daf-16 or its human orthologs plays a role in the development of impaired glucose tolerance condition, atherosclerosis or obesity.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973).

In instant case identification of candidate compounds that ameliorate or delay an impaired glucose tolerance condition, atherosclerosis or obesity by evaluating the expression of a polypeptide encoded by SEQ ID NO:54 (a domain of daf-16)or any variant thereof (like AFX or FKHR) is *not considered routine in the art and without sufficient guidance to the role of daf-16 domain and AFX or FKHR in the development of* impaired glucose tolerance condition, atherosclerosis or obesity *the experimentation left*

to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Objections

Claim 17 is objected to because of the following informalities: The instant claim recites claim limitation "a gene that hybridizes under stringent conditions to SEQ ID NO:54". It is noted that SEQ ID NO:2 is an amino acid sequence. Changing limitation "a gene that hybridizes under stringent conditions to SEQ ID NO:54" to "a gene that hybridizes under stringent conditions to the nucleic acid which encodes the amino acid sequences of SEQ ID NO:54" has been suggested. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to ***(571) 272-0547.***

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306.**

Sumesh Kaushal
Examiner GAU 1636

SUMESH KAUSHAL
PATENT EXAMINER